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Abstracts

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COMPLEX VISUAL HALLUCINATIONS IN THE ELDERLY WITH MACULAR DEGENERATION

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Objective: To evaluate the incidence and characteristics of complex visual hallucinations in an elderly population with visual impairment from macular degeneration.

Method: The study was carried out on 100 consecutive patients referred with visual impairments to the Low Visual Aid Clinic at the Royal Victoria Hospital. A detailed questionnaire was administered to each patient, including questions to elucidate their general health, alcohol-related or psychiatric problems. Questions regarding the nature of their ophthalmic disease, visual acuity and the time-course of their deterioration were also asked. Most importantly there were questions on the characteristics and frequency of any spontaneous visual phenomena they experienced.

Results: The patients had a mean age of 78.9 years with a visual acuity range of 6/12 part to 1/60. Females predominated. Thirty-four of the 100 patients experienced visual hallucinations of some type and 22 of these were complex (formed hallucinations) in type. Of those patients with complex hallucinations the most common percept was of animals of various types, and these were experienced by 12 patients. Other patients saw faces or people and a few patients saw inanimate objects.

Conclusions: We concluded that complex or formed visual hallucinations are a common phenomenon in elderly people with visual impairment from macular degeneration. Many patients discussed their experiences for the first time with us and were relieved not to be considered 'mad'. We felt that it would always be useful to question and reassure patients with blindness about spontaneous visual phenomena.

OPHTHALMIC FINDINGS IN FRAGILE X SYNDROME

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Method: We were able to trace 36 patients diagnosed as having Fragile X syndrome and to examine them for ophthalmic abnormalities.

Results: Of the 36 Fragile X syndrome patients (aged 3-50) (33 male: 3 female) studied in this survey, significant refractive abnormalities were found in 42%. These consisted mainly of anisometropic defects (11%) and astigmatism (14%). Most patients were hypermetropic (83%). Only one myopic patient was found (3%).

Significant ophthalmic abnormalities were found in 55% of the patients. Strabismus was present in 33% with slightly more esotropias than exotropias. Cataract was found in two of the older patients (6%). One patient had a major optic disc abnormality (3%) and another had congenital nystagmus (3%). Eight (22%) were photosensitive or avoided direct eye contact.

Conclusions: Although ophthalmic abnormalities are not diagnostic for the Fragile X syndrome, an awareness of the frequent association of Fragile X with hypermetropic astigmatism, anisometropia and strabismus may help lower the threshold of suspicion for the syndrome when investigating infants who are thought to be mentally retarded. Presenile cataract may occur more frequently than previously appreciated over the age of 40.

ANTICOAGULANTS IN CATARACT SURGERY

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The continuation of anticoagulants during cataract surgery is controversial. Several reports have suggested no change is required. A questionnaire

was sent to all European Eye Surgeons who had attended the European Society of Cataract and Refractive Surgeons Meeting in Amsterdam in 1995 enquiring about their approach.

Two-hundred-and-sixty-five questionnaires were analysed. Thirty-six per cent of respondents made no change. A further 36% stopped the anticoagulants. Twenty-two per cent altered their therapy to heparin, 2% gave a vitamin K injection and 4% altered the treatment according to the patient's general condition.

The following guidelines are suggested:

1. Check for International Normalised Ratio (INR) at least four hours prior to surgery to ensure the level is within the therapeutic range.
2. For patients who have a mechanical heart valve the INR should not be less than 1.8.
3. If anticoagulants must be discontinued, this should be done no longer than three days prior to surgery and recommenced on the day of surgery after cataract extraction.
4. A corneal section is advisable.

THE ROLE OF TACROLIMUS (FK506) IN THE TREATMENT OF POSTERIOR UVEITIS

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The efficacy and side-effects of Tacrolimus, a potent immunosuppressive macrolide antibiotic, have been assessed in the treatment of sight-threatening posterior uveitis. Five patients, who required systemic immunosuppression with Tacrolimus for control of uveitis, were followed. Three patients had Behçet's Disease, one had idiopathic retinal vaculitis and one had microscopic polyangiitis. Three patients were started on Tacrolimus as cyclosporin was failing to control their ocular inflammation and they were experiencing side-effects. Two patients were changed from cyclosporin to Tacrolimus due to cyclosporin toxicity. Two patients with Behçet's Disease showed a modest improvement in visual acuity in the affected eye and had no disease activity in the other eye. One patient with Behçet's Disease showed a marked improvement in best-corrected visual acuity from 1/60 to 6/24. The patient with microscopic polyangiitis was symptomatically improved and there was no progression of the posterior uveitis. The patient with retinal vasculitis showed regression of neovascularisation on Tacrolimus. Side-effects were less troublesome than with cyclosporin. It is concluded that Tacrolimus (FK506) has a useful role as an immunosuppressive agent for the treatment of posterior uveitis, especially in patients with cyclosporin intolerance or where cyoclosporin has failed to control the inflammation.

THE CONJUNCTIVAL IMMUNE RESPONSE TO ENCOUNTERED ANTIGEN

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Purpose: Immunomodulation via mucosa associated lymphoid tissue of gut and bronchus is a recently recognised concept. It is believed that tolerance is mediated by the CD8 + lymphocyte subset. The conjunctival mucosa can also induce tolerance to antigen instilled into the conjunctival sac but the cellular immune response in this tissue has not yet been studied. The purpose of our study was to determine the kinetics of lymphocyte subsets in conjunctival associated lymphoid tissue (CALT) induced tolerance.

Methods: Ten female adult Lewis rats were studied. Five rats (group 1) received one drop (5 µl) of retinal S antigen (500 ug/ml in phosphate buffered saline, PBS) instilled on to the lower forniceal conjunctiva twice daily for 10 consecutive days. Five rats (group 2) received PBS only and served as controls for the experiment. Two days after the last instillation the rats were sacrificed. The orbital tissue was snap frozen and embedded in cryomatrix. 5um sections were cut with a cryostat and prepared for immunohistochemical staining. A panel of monoclonal antibodies was used: CD3, CD4, CD8, CD25 and ED2. The number of positive cells were counted through the entire section including palpebral, forniceal and bulbar conjunctiva of both upper and lower eyelids.

Results: There was a significant increase in the number of CD8 + lymphocytes in the conjunctiva of animals receiving S antigen when compared to control animals ($p<0.02$).

Conclusions: Topical instillation of retinal S antigen causes a significant increase in the CD8 + lymphocyte subset in the conjunctival mucosa. This effect may be involved in the induction of tolerance to encountered antigen.

THE VALUE OF CORNEAL TOPOGRAPHY IN THE MANAGEMENT OF GRAFTED KERATOCONUS

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Objective: To assess the impact that corneal mapping has had on post-keratoplasty rehabilitation time and visual outcome in grafted keratoconic patients.

Methods: Records of 20 keratoconic patients who underwent penetrating keratoplasty (22 grafts) between 1992 and 1996 were identified and reviewed. Nine grafts were managed prior to corneal mapping being available and had suture removal guided by retinoscopy only. The remaining 13 had sequential corneal mapping as an intrinsic part of their management in planning selective suture removal.

Results: Selective suture removal assisted by corneal mapping improved post-operative management. The mean astigmatism at first definitive refraction was substantially reduced and all patients achieved corrected visual acuity of 6/12 or better. The mean time for visual rehabilitation was appreciably reduced. The number of interventions for refractive suture removal was similar for each group, but the removals in the mapping group took place over a shorter period of time.

Conclusions: Post-operative selective suture removal assisted by corneal mapping in keratoconic patients undergoing uncomplicated penetrating grafts allows more rapid visual rehabilitation and substantial reductions in post-operative astigmatism as measured at first definitive refraction.

THE DISTRIBUTION OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND ITS RECEPTORS IN OCULAR NEOPLASMS

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Purpose: To study the gene expression of vascular endothelial growth factor (VEGF) and its cognate tyrosine kinase receptors, Flt-1 and KDR, in intraocular tumours. Tumour-related alterations in VEGF/VEGF-receptor expression have also been examined in spatially separated, uninvolved retina of the same eyes.

Methods: Formalin-fixed archived eyes previously diagnosed as having retinoblastoma (n=10) or choroidal melanoma (n=10) were embedded in paraffin wax and sectioned. Non-neoplastic enucleated eyes were used as controls. Sections were processed for *in situ* hybridisation and probed using digoxygenin-labelled sense and antisense riboprobes to $VEGF_{165}$, Flt-1 and KDR.

Results: In neoplastic eyes, high levels of VEGF gene expression were observed within the vascularised regions of the tumours while the adjacent retina showed increased VEGF levels when compared to normals. Flt-1 and KDR gene expression occurred in VEGF-expressing cells in normal eyes while the endothelium of retinal blood vessels stained most strongly with Flt-1. Within the intraocular tumours, VEGF-receptor mRNA was evident in the endothelial cells and also in cells close to the vessels while in the adjacent retina, Flt-1 and KDR levels were elevated over normal, most strikingly in ganglion cells.

Conclusions: VEGF, Flt-1 and KDR are expressed by neural, glial and vascular elements within normal human retina. Intraocular tumours demonstrate a high level of VEGF and VEGF-receptor expression, however, within spatially separate retina in the same eyes; expression of these genes is also elevated. This increased expression of VEGF-receptors by several retinal cell types may be in response to high intraocular levels of VEGF, a phenomenon which could have relevance to neoplasm-related ocular neovascularisation pathologies.

MORBIDITY AND MORTALITY IN PATIENTS WITH OCULAR-MOTOR NERVE PALSIES

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We reviewed the notes of all cases of ocular motor nerve palsy that presented to this hospital 10 years ago. Twenty-five cases of idiopathic adult cranial nerve palsies were identified.

(VI = 17, III = 6, IV = 2). The patients were contacted again to record their subsequent medical history.

The most common risk factors known at the time of presentation were smoking, hypertension, ischaemic heart disease and stroke. The most common illnesses to develop were myocardial infarction and angina, but others included hyperlipidaemia, stroke, hypertension, peripheral vascular disease and diabetes.

Nine patients had died over the 10 year period. Using abridged life expectancy tables the normal years of life expectancy for each case was calculated based on age at presentation. Eight deaths occurred before what would be normally expected by an average of 2.8 years (one death occurred just as would be expected by the normal range tables).

In conclusion, we have identified that adult idiopathic ocular motor nerve palsies are associated with significant morbidity and mortality.

UTILISING POLYMORPHIC MARKERS IN THE GENETIC ANALYSIS OF DIABETIC RETINOPATHY

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Retinopathy is a vascular disease which primarily affects the capillaries and arterioles of the retinal circulatory bed. Individuals with NIDDM (Non-Insulin Dependent Diabetes Mellitus) or IDDM (Insulin Dependent Diabetes Mellitus) can be affected by this condition. While there are associations between hyperglycaemia and retinopathy, some individuals with very poor dietary control never develop retinopathy.

It is thus thought that there are genetic factors influencing the occurrence of retinopathy. In a Northern Ireland population we have examined "controls," individuals with diabetes (NIDDM or IDDM) for a long period of time (>16 years) who developed no signs of retinopathy; and "affecteds" who have severe retinopathy. Several gene families which may be important in determining retinopathy susceptibility were assessed for polymorphisms. Polymorphisms are variable DNA sequences which can be used to track the inheritance of a particular sequence of a chromosome through a family.

The nitric oxide synthase (NOS) gene family (vasodilators) and the endothelin (EDN) gene family (vasoconstrictors) were analysed for polymorphic regions. Numerous markers were determined for genetic analysis. The NOS genes in particular have several microsatellite (short repeat sequence) markers which are highly polymorphic. In the Northern Ireland patients both the NOS2 (inducible form) marker and the NOS3 (constituitive endothelial) marker were highly polymorphic. Preliminary data with these two markers suggest that there are more rare alleles appearing in the control population when directly compared to the affected individuals.

ADVANCED GLYCATION ENDPRODUCT FORMATION ON THE VITREOUS COLLAGEN NETWORK IS INCREASED DURING DIABETES AND HYPERGLYCAEMIA

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Advanced glycation endproducts (AGES) form irreversible crosslinks with long-lived proteins and have been shown to accumulate in tissues at an accelerated rate in diabetes. Using an AGE-specific ELISA we have investigated AGE formation in vitreous samples obtained after 3-port vitrectomy on non-diabetic and diabetic patients. In addition, we have utilised an *ex vivo* model of vitreous-AGE formation in which whole porcine vitreous humour was incubated in high glucose, high glucose with aminoguanidine, or normal saline for up to 8 weeks.

AGEs occurred at significantly increased levels in vitreous collagen from diabetics when compared to non-diabetic controls ($p<0.05$). As observed ultrastructurally using immunogold labelling, AGEs formed on porcine vitreous collagen fibrils after incubation in high glucose. Using SDS-PAGE and immunoblotting with type II collagen antibody, AGE-formation correlated with increased cross-linking of the high glucose-

incubated vitreous collagen while aminoguanidine inhibited this process. Furthermore, the molecular weight of vitreous hyaluronan decreased with glucose incubation, a phenomenon also inhibited by aminoguanidine.

This study suggests that AGEs form on vitreous collagen as a consequence of diabetes and hyperglycaemia. Advanced glycation and AGE-crosslinking of the vitreous collagen network and an accompanying shift in hyaluronan molecular weight may help to explain the vitreous abnormalities characteristic of diabetes.

THE EFFECT OF CHLOROQUINE ON RECEPTOR MEDIATED ENDOCYTOSIS IN RPE CELLS

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Receptor mediated endocytosis (RME) is a cellular function regulating the uptake of exogenous molecules from the environment via plasma membrane derived vesicles. Chloroquine has been reported to interfere with this function. This study investigates the effect of chloroquine on the RME of insulin in cultured retinal pigment epithelial (RPE) cells. 10 nm gold particles conjugated with insulin were presented to RPE cells in the presence or absence of chloroquine and the cells examined in the electron microscope. Preliminary results indicate that there is a depression of RME in the presence of chloroquine. Such inhibition of RME may reflect the ability of chloroquine to elevate the functional acidic pH of the endosome. Alkalisation of the endosome would interfere with normal receptor recycling and lead to depletion of insulin receptors at the plasma membrane.

SMALL VERSUS LARGER INCISION COMBINED CATARACT EXTRACTION WITH TRABECULECTOMY. HOW SUCCESSFUL ARE THEY?

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Small incision cataract surgery by phacoemulsification offers the theoretic advantage of reduced conjunctival dissection and decreased post-operative inflammation. These factors may reduce excessive wound healing and decrease the risk of subsequent filtering bleb failure in combined cataract extraction with trabeculectomy procedures. There is some evidence to indicate smaller scleral incision in combined procedures is associated with better intraocular pressure (IOP) control.

We reviewed our clinical experience of a consecutive series of patients who underwent combined larger incision (10 mm), n = 21, or small incision (5 mm), n = 23, cataract extraction with trabeculectomy. Success was defined as an IOP 5-21 mm/Hg range with or without glaucoma medications at one year follow-up and no additional glaucoma surgery. Ninety-eight per cent were successful, one patient requiring re-operation for IOP control. Fifty-seven per cent of large incision group and 91% of small incision group had IOP control without post-operative medication at one year follow-up. Mean IOP was similar during the first post-operative day and stabilised at 2-3 months follow-up in both groups. The complication rate was 33-43%. Posterior capsule opacification within one year of surgery and hyphaema were the most common complications.

Selection bias invalidates use of formal statistical comparisons between groups. While acknowledging this our study suggests small and larger incision combined procedures are effective in controlling IOP and restoring vision. Interestingly more patients had IOP control without medication in the smaller incision group which may suggest better filter functioning.

THE EFFECT OF CHLOROQUINE ON NITRIC OXIDE PRODUCTION IN RETINAL PIGMENT EPITHELIAL CELLS *IN VITRO*

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Retinal pigment epithelial cells (RPE) have been found to produce nitric oxide (NO) in response to cytokine exposure *in vitro*. NO is involved in a diverse range of physiologic and pathologic processes. It functions as a neurotransmitter, operates as a vasodilator, is involved in modulating inflammation and can oxidise many compounds. Chloroquine has a number of properties which may influence the production and action of NO in the RPE.

The effects of tumour necrosis factor-α (TNF-α), interferon-γ(IFN-γ) and lipopolysaccharide (LPS) on NO production in vitro were examined individually, in combination and in the presence

of chloroquine. Stimulation of NO production was achieved by a combination of the cytokines in the presence of chloroquine. However chloroquine appeared to inhibit the action of TNF-α.

These results show that although chloroquine may be able to inhibit the effect of individual cytokines on RPE cells, the combination of chloroquine with various cocktails of cytokines appears to promote NO release. This effect of chloroquine may be mediated through interference with the trafficking of cytokine receptors.

THE ROLE OF ADVANCED GLYCATION IN DIABETIC RETINOPATHY

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The pathogenesis of diabetic retinopathy remains largely unknown, although advanced glycation endproducts (AGEs), formed from the nonenzymatic glycation of proteins and lipids with reducing sugars, have been implicated in many diabetic complications. Recent studies suggest that the cellular actions of AGEs may be mediated by AGE specific receptors (AGE R). We have examined the immunolocalization of AGEs and AGE-Rs in the retinal vasculature of streptozotocin (STZ) diabetic (Db) rats at 2, 4 and 8 months post-induction as well as non-diabetic rats (infused with AGE-Albumin for 2 weeks). Age and sex matched non diabetic rats and a group which had been injected with unmodified albumin were also examined. The retinae were sectioned or the vasculature was isolated by trypsin digestion. Using a monoclonal antibody specific for AGEs and polyclonal antibodies raised against the AGE-receptor proteins, immunoreactivity (IR) was examined in the complete retinal vascular tree. In diabetic rats, there was a progressive increase in AGE-IR after 2 and 4 months of diabetes, with most AGEs appearing basement membrane (BM) associated. After 8 months of diabetes, rats showed intense AGE-IR in the pericytes, smooth muscle, endothelium and BM of the retinal vessels. In AGE-infused rats, AGE-IR was most intense in smooth muscle cells and pericytes, while generally, the BM was much less immunoreactive than in the Db group. The retinae of normal and albumin infused rats were largely negative for AGE-IR. AGE-Rs were localized to the vascular endothelium, pericytes and smooth muscle of normal rat retinae, and this distribution did not alter with AGE infusion or diabetes. This study indicates that retinal vascular smooth muscle cells and pericytes preferentially accumulate AGEs after long term diabetes or short term AGE infusion. The co-localisation of AGEs and AGE-Rs in the retinal vascular cells suggests that a receptor mediated interaction with AGEs may be involved in the pathogenesis of diabetic retinopathy.

LOCALISATION OF A GENE FOR CENTRAL AREOLAR CHOROIDAL DYSTROPHY TO CHROMOSOME 17P

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Central areolar choroidal dystrophy (CACD) is a rare inherited retinal disease which causes progressive profound loss of vision in patients from their 4th decade onwards. We have identified a Northern Ireland family with eighteen affected individuals in 3 living generations. We have performed a total genome search and demonstrated linkage of CACD in this family to chromosome 17p (multipoint Zmax = 6.3 at D17S1832). The genes for phosphatidylinositol transfer protein (PITPN), retinal guanylate cyclase (GUC2D), β-arrestin 2 (ARRB2), pigment epithelium-derived factor (PEDF) and recoverin (RCV1) map to this region and are candidate genes for retinal disease. Analysis of the coding region of the PITPN, GUC2D and PEDF genes failed to reveal any mutations in this family. The ARRB2 and RCV1 genes were excluded as the cause of CACD by fine mapping of the critical CACD gene locus.

The mapping of CACD to this region represents a new locus for this disease. It demonstrates that CACD may be genetically heterogeneous and provides a new locus for candidate genes for macular dystrophies and also for age related macular degeneration.

VISUAL EVOKED POTENTIALS AND STEREOPSIS IN DUANE'S SYNDROME

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Patients with Duane's Retraction Syndrome have restricted eye movements, but many of them are able to maintain binocular function by using an abnormal head posture to compensate for this. This study has examined whether this has any effect on the development of binocular visual function.

Visual acuity, stereoacuity and eye movements have been studied and binocular beat VEPs recorded in 10 patients with Duane's Syndrome and 10 age-matched normal control subjects. The patients with Duane's Syndrome were found to have reduced stereoacuity compared to the normal group. (TNO mean 80 sec of arc c.f. 37.5 sec of arc. Titmus mean 143 sec of arc c.f 44 sec of arc). The binocular beat VEPs showed that the difference beat response at 2 Hz was significantly reduced in the patients with Duane's Syndrome compared to the normal age-matched group (mean signal-to-noise ratio 2.40 ± 1.05 c.f 4.30 ± 2.66; $t = 2.21$, d.f = 18, $P<0.05$). Although many patients with Duane's Syndrome maintain binocular single vision by using an abnormal head posture they have reduced stereoacuity and show electrophysiological evidence of reduced cortical binocularity. This indicates that the restricted eye movements in this condition affect the development of cortical binocular function.

STEREOLOGICAL ANALYSIS OF CHANGES IN RETINAL CAPILLARIES DURING DIABETES AND THE EFFECT OF SULINDAC TREATMENT

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Stereological analysis was used to determine early quantitative changes in the 3-dimensional structure of retinal capillaries during diabetes and following treatment with sulindac (a non steroidal anti inflammatory drug and inhibitor of aldose reductase activity).

Experimental diabetes was induced in 22 male beagle dogs by a single injection of an alloxan/ streptozotocin mixture and blood glucose levels maintained at 15-20 mmol/l. Sulindac (10 mg/ kg) was administered daily to 12 dogs chosen at random from the diabetics. After 4 years duration of diabetes all the diabetic animals together with 8 age-and sex-matched controls were sacrificed, the eyes enucleated and processed for transmission electron microscopy. Stereology was then carried out to estimate quantitative morphological changes in the retinal capillaries (Anderson et al. 1994). Results show that the total volumes of retinal capillaries and capillary basement membrane as well as the total surface area of basement membrane were significantly increased in the untreated diabetics compared to the sulindac treated-diabetics or controls ($p \leq 0.05$). There was no significant difference in the above stereological parameters between the sulindac-treated diabetics and the controls.

Biochemical analysis showed that there were no significant differences in the red blood cell levels of sorbitol between the sulindac-treated diabetics and the untreated diabetics. Also, sulindac treatment did not affect the increased levels of fructoselysine (a glycation product) or N^{ϵ}-(carboxymethyl) lysine (an advanced glycosylation end product, AGE) which occur in the untreated diabetics, nor was there any significant differences in the total antioxidant potential or levels of malondialdehyde between the sulindac-treated and the untreated diabetics.

This study shows that, while sulindac treatment prevents the development of some of the early morphological changes which occur during the development of diabetes, it does not inhibit aldose reductase activity or the formation of AGES, nor does it affect oxidative stress.

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THE EFFECT OF INCREASED INTRATHORACIC PRESSURE ON PULSATILE OCULAR BLOOD FLOW

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Purpose: To determine whether increased

intrathoracic pressure affects the Pulsatile Ocular Blood Flow (POBF) in healthy subjects.

Methods: POBF was measured using a pneumotonograph (OBF systems UK). Subjects were evaluated while achieving a steady expiration at 20 mmHg (and where possible 40 mmHg) using a mouth-piece attached to an aneroid manometer. Values were obtained for ocular Pulse Amplitude PA, intraocular pressure IOP and POBF.

Results: There were twenty subjects in the age ranges 20-34, 35-49, 50-64 and 65-80 years. A significant decrease in PA and POBF was noted. This appears to be proportional to the elevation of intrathoracic pressure. At 20 mmHg the mean reduction in POBF was 33% (56% reduction at 40 mmHg). PA was reduced by 44% at 20 mmHg (60% reduction at 40 mmHg). The IOP response varied as a function of age, tending to rise in younger subjects but falling in the older group.

Conclusions: These results show profound changes in POBF and PA in response to moderate fluctuations of intrathoracic pressure. These may reflect changes in central venous pressure and/or alterations in autonomic tone. Information on the ocular blood flow response to this stressed cardiovascular state may be helpful in evaluating ocular blood flow regulation in glaucomatous eyes.